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On eukaryotic intelligence: Signaling system's guidance in the evolution of multicellular organization

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A B S T R A C T

Communication with the environment is an essential characteristic of the living cell, even more when considering the origins and evolution of multicellularity. A number of changes and tinkering inventions were necessary in the evolutionary transition between prokaryotic and eukaryotic cells, which finally made possible the appearance of genuine multicellular organisms. In the study of this process, however, the transformations experimented by signaling systems themselves have been rarely object of analysis, obscured by other more conspicuous biological traits: incorporation of mitochondria, segregated nucleus, introns/exons, flagellum, membrane systems, etc. Herein a discussion of the main avenues of change from prokaryotic to eukaryotic signaling systems and a review of the signaling resources and strategies underlying multicellularity will be attempted. In the expansion of prokaryotic signaling systems, four main systemic resources were incorporated: molecular tools for detection of solutes, molecular tools for detection of solvent (Donnan effect), the apparatuses of cell-cycle control, and the combined system endocytosis/cytoskeleton. The multiple kinds of enlarged, mixed pathways that emerged made possible the eukaryotic revolution in morphological and physiological complexity. The massive incorporation of processing resources of electro-molecular nature, derived from the osmotic tools counteracting the Donnan effect, made also possible the organization of a computational tissue with huge information processing capabilities: the nervous system. In the central nervous systems of vertebrates, and particularly in humans, neurons have achieved both the highest level of molecular-signaling complexity and the highest degree of information-processing adaptability. Theoretically, it can be argued that there has been an accelerated pace of evolutionary change in eukaryotic signaling systems, beyond the other general novelties introduced by eukaryotic cells in their handling of DNA processes. Under signaling system's guidance, the whole processes of transcription, alternative splicing, mobile elements, and other elements of domain recombination have become closely intertwined and have propelled the differentiation capabilities of multicellular tissues and morphologies. An amazing variety of signaling and self-construction strategies have emerged out from the basic eukaryotic design of multicellular complexity, in millions and millions of new species evolved. This design can also be seen abstractly as a new kind of quasi-universal problem-solving 'engine' implemented at the biomolecular scale—providing the fundamentals of eukaryotic 'intelligence'. Analyzing in depth the problem-solving intelligence of eukaryotic cells would help to establish an integrative panorama of their information processing organization, and of their capability to handle the morphological and physiological complexity associated. Whether an informational updating of the venerable "cell theory" is feasible or not, becomes, at the time being – right in the middle of the massive data deluge/revolution from omic disciplines – a matter to careful consider.

1. Introduction: The distinctive problem solving capabilities of eukaryotic cells

The main goal of this paper is to continue a previous effort focused on the signaling "intelligence" of the prokaryotic cell (Marijuán et al., 2010), which is now addressed towards the eukaryotic camp. Actually, both papers may be taken as a single attempt to review the whole molecular apparatuses in charge of organizing the systematic relationships that any living cell has to maintain with its inner/outer environment. Amidst the bewildering variety of

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molecular components and signaling pathways of eukaryotes, and their dense connection with the rest of cellular subsystems, we will see that a new discussion on the hallmarks of cellular intelligence, biocomputationally updating the venerable "cell theory" (framed by T. Schwann, M. Schleiden, and R. Virchow almost two Centuries ago), and its amendment by the "Central Dogma" in the 60s, could be framed. Perhaps, in the same way than a new field of "artificial intelligence" was launched decades ago stemming out from the processing capabilities of computers, the bio-informational capabilities of cells would nowadays demand their own multidisciplinary arena.

At stake is whether the reflections of theoretical biology are keeping pace with the phenomenal accumulation of empirical/computational data taking place. Cellular signaling systems have been the subject of countless works in last two decades, either molecularly, computationally, systemically or synthetically, but always focusing on some particular pathways or networks, and very few works have attempted the description of an integrative panorama or drafted the large-scale insights needed to comprehend their evolutionary trajectory. Whether it is a plausible task or not, given the outmost complexity and heterogeneity of eukaryotic signaling, is another matter. Nevertheless even an imperfect synthesis may be a useful resource in a field which has to be trodden by researchers and scholars from a number of disciplines. Needless to say, the authors are well aware of the famous Schrödinger's warning:

> I see no other escape from this dilemma (lest our true aim be lost forever) than that some of us should venture to embark on a synthesis of facts and theories, albeit with second hand and incomplete knowledge of some of them—and at the risk of making fools of ourselves. (cited in Stonier, 1990).

What is distinctive in eukaryotic signaling systems? Being itself a 'composite' of other cellular systems, the eukaryotic cell was forced to handle its inner organization of processes in new ways that later on allowed a far more effective problem solving, to be based on specialization of cell types and communication through multiple pathways–networks. We might argue that prokaryotes had already used some of those very capabilities, or at least their incipient evolutionary traits, mainly towards the direct solution of *molecular assimilation* problems (in their encounter with environmental substances); while eukaryotes were to achieve a fascinating developmental complexity by evolving towards a quasi-universal solution of *molecular organization* problems. Explaining away this difference involves a new interpretation of cellular organization, but not only in evolutionary-biological terms, "computer terms" also become necessary, or better, a new "informational" explanatory ground should be established. As we will argue, the tight coupling among transcription, alternative splicing, domain recombination, and cell differentiation, all of them under signaling system's guidance, integrates an abstract problem-solving 'engine' that transcends the biomolecular realm. Rather than following analogies with Turing machines Danchin (2009) or with operating systems (Yan et al., 2010), we will discuss the eukaryotic self-construction and communication capabilities in a new way, starting from von-Neumann's views of self-constructing machines (Vedral, 2010). This discussion will be addressed later on, at the end of the paper, once the evolution, structure, aggregated functioning, and classes of pathways of eukaryotic signaling systems have been drafted.

Evolutionarily, the complexity of eukaryotic signaling – which excels in the electromolecular operations of nervous systems – did not arise from scratch. A good portion of the new signaling system was directly inherited from prokaryotes, but many other parts were invented through *bricolage* and were cobbled together with highly complex controlling apparatuses unrelated to prokaryotes. Functionally speaking, however, the relative simplicity attributed to prokaryotic cells is only apparent, at least concerning their signaling capabilities. As was discussed in a previous publication (Marijuán et al., 2010), these cells have only three main classes of component-system arrangements for signaling purposes; but they are instantiated in about *one or two hundred* different pathways for each cell, acting as independent or colligated channels for the entrance of external information. In contrast, the cells of complex eukaryotes, such as vertebrates and mammals, are endowed with several dozen classes of component-system arrangements (main signaling pathways), but they comprise *thousands* of specific molecular implementations in different tissues, particularly within the nervous system. Amidst all that complexity, however, there is a deep evolutionary sense and coherence in the way signaling pathways have been assembled in eukaryotes and particularly in the functions they perform for the development and physiology of the multicellular organism. Appropriately interrelating such diversity and coherence will be the goal of this paper.

Essentially, the cellular signaling system is in charge of receiving and interpreting the signals that the whole organism instantiates, and of modifying accordingly the developmental/physiological trajectory followed by the concerned cell. As we will see, an overabundance of transmembrane molecular mechanisms are continuously sensing the external milieu, subsequent amplification cascades are conducing and networking the external changes registered, and finally quite many different actuators are mobilized—often transcription factors and associated proteins in the nucleus, but also many other molecules in the cytoplasm. Along the differentiation process, the cell changes its state and advances its life cycle by continuously following the incoming signals from the whole organism, mixing them with its own inner controlling mechanisms. In a curious parallel with the nervous system, it is the signaling system itself which instructs the cell about what are the specific external/internal signals to follow—in theoretical biology both are considered as "anticipatory systems" (Rosen, 1985). When the cell changes its state or differentiates, its own signaling system changes subsequently, but it has already been changed beforehand and has prepared the cell to distinguish the appropriate signals from the non-pertinent ones. This guidance mission of signaling systems both on cellular self-construction and on evolutionary grounds is one of the central ideas of this paper.

In the sections which follow, we will discuss first about evolutionary origins, on why a plethora of signaling resources was evolved and how a recombination strategy was mainly followed in the assemblage of this crucial system (Section 2). Subsequently we will examine in detail the "four roots" of eukaryotic signaling: detection of solutes, detection of solvent, cell-cycle control, and the combined system of endocytosis and cytoskeleton (Section 3). Further, a chart of the main eukaryotic signaling paths will be produced (Section 4), including a prototypical pathway scheme, a functional grouping of the pathways with a simplified classificatory attempt of their roles in development and physiology (21 pathways and pathway's classes described in Table 1). A brief examination of neuronal signaling as a prototype of signaling complexity will take place in Section 5, where a number of signaling pathways will be described, concretely at the postsynaptic site of glutamatergic excitatory neurons. Finally, in Section 6, the discussion about signaling and the problem-solving organization of the eukaryotic cell will be retaken; some hints will be introduced about a new informational theory on cellular self-constructing intelligence.

2. How signaling resources were evolved in the transition from prokaryotic to eukaryotic

An information revolution took place in cellular systems around 1200 Mys ago. It was preceded and made possible by an energy revolution derived from the symbiotic capture of mitochondria, as